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Studying Ligand Binding on HNE

Human neutrophile elastase (HNE) is an enzyme chiefly used to defend against foreign proteins, but when overabundant can degrade healthy tissue and cause a variety of diseases. Therefore it is desirable to seek HNE inhibitors. In this study, ligand docking calculations and molecular dynamics (MD) simulations were used to model the inhibitory action on HNE by various ligands, with the molecular mechanics-Poisson Boltzmann-surface area (MM-PBSA) method used to calculate structural free energies. When simulated in MD runs of 2 ns, many ligand-HNE complexes exhibited instability, which suggested weak binding. The two ligands found to bind most effectively, bornyl caffeate and fukinolic acid, were each given 30 docking placements divided into groups according to their general docking formation.

On each placement group, MD simulation runs of 1 ns were performed. This was done for bornyl caffeate, fukinolic acid, and closely related compounds. The most stable ligand-protein complexes were further analyzed by thermodynamic integration (TI) calculations to find their binding free energies. These agreed more closely with experiment for bornyl caffeate and its derivatives than for fukinolic acid and its derivatives, and the MD simulation analysis found a prospective binding mode for bornyl caffeate. Bornyl ferulate, a derivative of bornyl caffeate formed by replacing the meta-hydroxy with a methoxy group, was found to bind more strongly to HNE when the methoxy group was transferred to the other side of the aromatic ring. In addition, caffeic acid was found to bind significantly more weakly to HNE than bornyl caffeate, confirming the importance of ligand hydrophobicity for the purposes of binding to proteins in general and HNE in particular.

There are some notable advantages as well as drawbacks to this analytical method. The combination of techniques did discover a possible binding mode for bornyl caffeate within HNE, and demonstrated the ability to propose binding modes for bornyl caffeate derivatives (for instance, the modified conformation of bornyl ferulate). On the other hand, the analysis failed to find a binding mode for fukinolic acid, a compound which is known to bind well to HNE experimentally; additionally MM-PSBA is currently impractical for comparing binding free energies of similar placements for differing ligands,

since the differences between these free energies (1—2 kcal/mol) are roughly equal to the statistical error (1 kcal/mol) of the MM-PSBA method.

* Steinbrecher, T.; Case, D. A.; Labahn, A. A Multistep Approach to Structure-Based Drug Design: Studying Ligand Binding at the Human Neutrophil Elastase. *J. Med. Chem.* **2006**, *49*, 1837-1844.